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HENRY FORD HEALTH SYSTEM IRB PROTOCOL FORMAT

Appendix 1

(Incomplete applications will be returned, & inadequate responses may lead to a delay in review.)You may mark your responses in the shaded areas following each question. Supporting documents (articles, drug toxicity information, etc.) must be submitted when applicable. A "See Attached" response will not be accepted for review. Be concise & clear.

Directions:

Sponsored protocol: If you have a sponsored protocol (e.g., pharmaceutical), a grant application (e.g., National Institutes of Health), or another peer-reviewed protocol, you may submit that protocol/application along with the application elements. It is the responsibility of the Principal Investigator to assure, however, that the protocol/application contains the information requested in this "IRB Protocol Format". Additional sheets should be attached to the protocol/application as necessary to provide the information (e.g., a description of the process of consent) required for IRB review. When available, the Investigator's Brochure must be submitted along with the research protocol, or a summary of the preclinical/animal data and any relevant clinical data.

Physician Initiated protocol: If you have not been provided a protocol from an outside source, you must develop one. The following is the "Henry Ford Health System "IRB Protocol Format".

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1. **PURPOSE:** State in one or two sentences the purpose or objective of this project. **The purpose of this project is to compare the effectiveness of two different but well accepted routes of administration of tranexamic acid in order to reduce blood loss and need for transfusion in patients undergoing lumbar spine surgery. Specifically, this study seeks to identify if intravenous tranexamic acid is superior to oral tranexamic acid in reducing blood loss and need for transfusion.**

2. **SPECIFIC AIMS:** Number your aims so that the aims can be referred to in the Project Design and Data Analysis sections of this outline.
   1. **compare intra-operative blood loss between the two groups**
   2. **compare post-operative drop in hemoglobin between the two groups**
   3. **compare post-operative blood loss between the two groups**
   4. **compare number of units transfused between the two groups**
   5. **compare post-operative drain output between the two groups**
   6. **compare incidence of thromboembolic events between the two groups**

3. **RATIONALE FOR THE PROJECT:**
   a. State the rationale for the project and support it with background information about the project. Critically evaluate existing knowledge, and specifically identify the gaps in knowledge the project will fill. **Spine surgery is associated with large amount of perioperative blood loss. Factors influencing blood loss include surgical technique, operative time, number of vertebral levels arthrodesed, and others. Significant blood loss is associated with complications such as hypotension, end organ damage, or coagulopathy. Blood transfusions can increase risks of infection, blood incompatibility, and allergic reactions. Due to the significant risks and complications associated with blood loss and allogenic transfusions, efforts to identify safe and effective ways of lowering blood loss during spine surgery are crucial. Many methods have been utilized to reduce allogenic blood transfusions, such as autologous blood predonation, antifibrinolytic drugs, acute normovolemic hemodilution, intraoperative blood salvage, and others. Furthermore, the administration of antifibrinolytics, such as tranexamic acid (TXA) and epsilon-aminocaproic acid (EACA), has been shown to reduce bleeding in cardiac, gynecological, urologic and total joint replacement surgeries. There have been many published studies investigating various antifibrinolytic agents such as TXA, EACA, and aprotinin. While aprotinin was shown to increase mortality rate in patients following cardiac surgery, TXA and EACA have not been shown to cause any substantial morbidity or to increase rate of thromboembolic events. Although IV TXA has been shown to be effective in reducing blood loss and transfusions in patients undergoing spine surgery, no studies in the literature have investigated the efficacy of PO TXA in decreasing blood loss and transfusions. We believe that PO TXA will be just as efficacious and more cost-effective in reducing blood loss and transfusion needs in patients undergoing lumbar spine surgery.**

   b. State the applicant's prior research and experience in this research area. **The PI has performed research involving spine surgery, however has not performed previous studies looking at tranexamic acid.**

4. **SIGNIFICANCE:** State concisely the importance of this project by relating the purpose to broader, long-range objectives. **The ultimate goal is identifying the most cost-effective protocol to decrease blood loss and need for transfusion. Oral TXA costs about $14 compared to the 4x-8x more expensive version of IV TXA, depending on the final IV formulation. If oral TXA is found to be as efficacious as IV TXA in reducing blood loss and need for transfusion, significant cost savings can be achieved for the patient and the health care system in general.**

5. **SUBJECTS IN THE PROJECT:**
   a. State the inclusion and exclusion criteria for enrollment of subjects.**All adult patients over age 18 and scheduled for open lumbar spine surgery at Henry Ford Hospital Main (Detroit, Michigan, United States) and West Bloomfield (West Bloomfield, Michigan, United States) will be eligible for the study. Exclusion criteria includes known allergy to TXA, history of renal failure or kidney transplant, a history of arterial thromboembolic event (eg. myocardial infarction, stroke) within the past year, placement of an arterial stent within the past year, a history of thromboembolic event, or refusal to receive blood products.**
   b. Describe the control population (if utilized) and justify its selection.**Controls will not be utilized.**
   c. Support the likelihood of recruiting the number of subjects required to complete the project. Relate this to other projects recruiting similar subjects. **Inclusion of the patient population of 3 spine surgeons creates a high likelihood of adequate patient recruitment. Other randomized controlled clinical trials involving IV TXA consistently meet minimum participation for adequate power analysis. There have been similar trials in the past that successfully recruited similar if not more patients without difficulty. We are currently doing approximatley 5-8 open lumbar spine surgeries a week. We are aiming to enroll 15-20 per month in the study as a conservative projection. Therefore, we do not anticipate any difficulty in recruiting patients.**

6. **PROJECT DESIGN AND PROTOCOL:**
   a. Describe the experimental design/methodology.**This is a prospective randomized controlled trial.**
   b. Outline the protocol, corresponding it to the specific aims; identify the data or endpoints to be analyzed to reach the specific aims.**Patients will be consented and recruited according to the inclusion and exclusion criteria described above at their preoperative visit 1-2 weeks prior to their scheduled surgical date. Once participation has been determined and consent obtained, patients will be randomized with a computer-generated table. Randomization will be stratified by gender and number of vertebral levels arthrodesed. The oral TXA group will receive 1950 mg TXA (3 tablets of 650 mg) approximately 2 hours before incision. The IV TXA group will receive the standard dosing for our institution of 1 g TXA (diluted in 100 mL normal saline) given as an IV bolus immediately before incision and another 1 g TXA given before closure. Patient demographic and preoperative characteristics will be documented for comparison between the treatment groups. All patients will have nightly labs including a complete blood count (CBC), and their drain outputs will be recorded. The recorded characteristics will include the following: age, sex, American Society of Anesthesiologists' physical status classification, weight, height, BMI, and pertinent preoperative laboratory values (prothrombin time/international normalized ratio [PT/INR], platelet count, hematocrit, and hemoglobin). The primary outcome measure of the study is postoperative drop in hemoglobin, which is calculated as the preoperative hemoglobin minus the patient's lowest postoperative hemoglobin. Secondary outcomes are estimated blood loss (EBL), postoperative blood loss, postoperative hemoglobin loss, drain output, number of blood units transfused, and thromboembolic events. Postoperative blood and hemoglobin loss are calculated as a function of patient characteristics including sex, weight, and height as well as preoperative and postoperative hemoglobin balance according to Nadler et al and Good et al. All outcome measures are recorded after the patient is discharged from the hospital by a research assistant, who is not involved in the clinical management of the study participants. The transfusion protocol is planned for a hemoglobin level of less than 7.0 g/dL.**
   For males: BV = 0.3669*(Height in meters)^3 + 0.03219*(Weight in kilograms) + 0.6041
   For females: BV = 0.3561*(Height in meters)^3 + 0.03308*(Weight in kilograms) + 0.1833
   Hbloss = BV*(Hbi-Hbe)*0.001 + Hbt
   Blood loss = 1000*(Hbloss/Hbi)
   Hbloss = Hemoglobin loss; BV = Blood Volume; Hbi = initial Hgb; Hbe = ending Hgb; Hbt = transfused Hgb = about 52g (SD 5.4g) per 1u pRBC (320mL)

Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. Surgery 1962;51:224.
Good L, Peterson E, Lisander B. Tranexamic acid decreases external blood loss but not hidden blood loss in total knee replacement. Br J Anaesth 2003;90:596.

c.

d. Discuss potential limitations and difficulties in the protocol.**No major limitations or difficulties anticipated.**

e. Provide a tentative schedule for conducting and completing this project and, if applicable, the multicenter study.**If IRB can be accepted by Jan or Feb, patient enrollment can begin at that time. We are expecting that after obtaining consent and inclusion/exclusion criteria 15 - 20 patients per month will enroll in the study. Therefore we are predicting at least 6 months for completion of data collection and manupscript preparation. Consent may be more difficult to obtain, and therefore data collection may last up to one year.**

f. Data collection: **Submit a copy of the data collection tool or list the data fields to be collected (review IRB policy, *Access to Medical Records for Research*).Data fields to be collected: intra-operative blood loss (EBL), post-operative drop in hemoglobin, post-operative blood loss between the two groups, number of units transfused, and number of thromboembolic events.**

7. **DATA ANALYSIS:** Describe the analysis of the data and relate this to the specific aims in detail. Case reports and medical record reviews also require a description of the planned data analysis (ie. descriptive, observational). The Committee recommends free consultation with the Division of Biostatistics and Research Epidemiology *before* IRB submission. **Data analysis will consist of summary statistics between the two patient groups. Intention to treat analysis will be employed when comparing the two arms. Potential confounders will be identified including demographic and functional data. This will be a non-inferiority trial to show PO TXA will be as efficacious as IV TXA. Means and standard deviations will be computed. Student t test will be used to statistical analysis. P<0.05 will be considered statistically significant.**

8. **JUSTIFICATION FOR NUMBER OF SUBJECTS OR DATA:**

a. State the number of subjects or data points to be analyzed in the project at this institution and the total number for multicenter studies. The Committee recommends consultation with the Division of Biostatistics and Research Epidemiology (313) 874-6360. **A total of 60 patients will be enrolled in this study**

b. *Describe the statistical justification for this number of subjects or data points.* ***The standard deviation from the current literature on hemoglobin change was 1.25 g/dL and was used for the power analysis. Using a clinically relevant difference of 1.0 g/dL, we chose our equivalence margin as ±1.0 g/dL with alpha at 5% and 80% power. Testing equivalence of hemoglobin change between groups, it was determined that a sample size of 29 subjects per group or 58 total subjects were needed. Therefore, we aim to enroll 60 patients (30 in each group) in our study.***

c.

FORM A

HENRY FORD HEALTH SYSTEM (IRB) DRUG/SUBSTANCE INFORMATION

(This form must be completed for each individual drug or substance *-investigational or marketed-* that is being administered as part of this research study)

1. Generic/Chemical Name: **Tranexamic acid**	2. Trade Name: **Lysteda**
3. Manufacturer:	4. Mode of Administration: other: **PO and IV**
5. How Supplied (dose form & strength): **PO: 650mg tablets; IV: 1g diluted in 100mL normal saline**	6. Who will be administer the drug/substance? **Pre-op nurses or anesthesiologist/CRNA**
7. Dosage and Schedule Proposed: **PO: 1950 mg (3 tablets) in preop; IV: 2g total (1g before incision and 1g before closure)**	
8. Will you be utilizing research pharmacy for storage or dispensing of any medication? (if this is an inpatient study, you are required to use research pharmacy). ☒ Yes ☐ No	